Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-48 are pending in the application, with claims 1 and 48 being the independent claims. Claims 34-39 have been withdrawn from consideration as being directed to a non-elected invention. New claim 48 is sought to be added. The changes to claim 1 and dependent claim 22 are made to clarify its subject matter. Support for these changes can be found, for example, in originally presented claim 1 and in the Description at page 2, in the last full paragraph. Support for the term "covalent bonds" can be found, for example, in the Description at page 3, in the last full paragraph. Support for addition of the term "one or more covalent bonds" can be found, for example, in the Description on page 5, third full paragraph where it is disclosed that detergent molecules are dimerized or oligomerized. Support for the change of the term "function" to "functional group" in claims 3, 4, 6, and 7 can be found in the Description, for example, at pages 4 and 6 (first full paragraphs). On page 6 of the Description, several functional groups, referred to as "functional residues" are exemplified. Addition of the term "upon reaction with an amine" in claim 4 is supported on page 6, first full paragraph of the Description. It is clear from this paragraph that a halogen on an ethylene residue is being exchanged with a reactant amine group. Amendments were made to claims 5, 8, 9, and 10 to correct typographical errors or to clarify the claims. Deletion of the term "preferably" in claim 8-11 is made to clarify the subject matter of the claim. Support for the addition of the term "linked via one or more covalent bonds" in claims 27-29 can be found in the Description, for example, towards the top of page 22. Support for respectively changing the term "function" or "functions"

to "functionality" or "functionalities" in claims 27-31, 46 and 47 can be found in the Description, for example, at page 22 in the second paragraph where these terms are used interchangeably. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Restriction Requirement

A provisional election was made with traverse to prosecute Group I, claims 1-33 and 40-46. This election is made without prejudice to or disclaimer of the other claims or inventions disclosed. Applicants reserve the right to file one or more divisional applications to the non-elected inventions should the restriction requirement be made final. Applicants respectfully traverse the restriction requirement.

The Examiner identified groups I and II as having the relationship of combination and subcombination respectively. *See* M.P.E.P. (Eighth) § 806.05(c) (2001). Restriction is proper in this situation if two-way distinctness can be demonstrated. *See Id.* However, the Examiner misconstrued the relationship amongst the claims. Group I, claims 1-33 and 40-46, is drawn to a transfection particle comprising one or more nucleic acid molecules ionically associated with identical or different covalently linked precursor molecules, its method of preparation or use, pharmaceutical formulation, or a kit containing the same. Group II, claims 34-39 and 47 (all ultimately dependent upon claim 1 of Group I), is drawn to the same transfection particle *in combination with* an

endosomolytic functionality. Thus, if the claims must read on a subcombination/combination relationship, Applicants respectfully urge that Group I is a subcombination and Group II is a combination.

Restriction is not proper because two-way distinctness cannot be demonstrated between these claim groupings. In particular, it cannot be shown that the combination claims do not require the particulars of the subcombination as claimed. Here, the combination claims of Group II are all ultimately dependent upon subcombination claim 1 of Group I . Therefore, the combination claims *do* require all the particulars of the subcombination as claimed in group I.

Alternatively, even if it is deemed that patentably distinct inventions appear in Applicants' application, restriction remains improper because the Examiner has not shown that the search and examination of the groups would entail a "serious burden". *See* M.P.E.P. (Eighth) § 803 (2001). In the restriction requirement, the Examiner has indicated that both groups would be classified in class 935, subclass 54. Paper No. 11, page 2. Thus, examination for either group would require the same search. Moreover, the claims of Group II only add the endosomolytic function and various embodiments thereof. Even if these functions render the claims of Group II as patentably distinct, they hardly represent a burden on the Examiner for further searching.

Applicants respectfully request reconsideration and withdrawal of the restriction requirement.

II. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 8-18 under 35 U.S.C. § 112, first paragraph. Paper No. 11, page 7. In particular, the Examiner alleges that

> the specification . . . does not reasonably provide enablement for the claimed molecules with recited functionalities claimed in the instant invention represented by general formula I recited in claim 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Id. The Examiner has also rejected claims 42-44 under 35 U.S.C. § 112, first paragraph on the grounds that the Description does not enable one skilled in the art to make and/or use the invention as claimed. Paper No. 11, page 10.

Applicants respectfully traverse this rejection on two grounds: 1) the Examiner is requiring more disclosure than is legally required to enable an invention, and 2) the Examiner has not met her burden of making a *prima facie* showing that these claims are not enabled.

A. Legal Standard for the Enablement Requirement

The federal courts have provided guidance for determining whether a description is enabling relative to the scope of the claims. The enablement requirement of 35 U.S.C. § 112, first paragraph "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). This notion was later repeated: "The relevant inquiry [is] whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims." *In re Moore*, 169 USPQ 236, 239 (CCPA 1971). Thus, the description need not enable more than the scope of the claims.

In order to enable the claimed invention as required by 35 U.S.C. § 112, first paragraph, the specification need only enable a person of ordinary skill in the art to (i) make the claimed composition of matter and (ii) practice *a single use* of the claimed composition of matter without undue experimentation.[1] The M.P.E.P. also provides guidance for the latter requirement:

> . . . when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. . . . if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

M.P.E.P. (Eighth) § 2164.01(c) (2001). Thus, for composition claims, the description only needs to enable one use.

Moreover, there is a presumption that an application is enabling. A patent applicant's specification disclosure which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d. 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). This judicial holding is reflected by USPTO procedural guidance for examiners. In particular, examiners bears the initial burden of making a *prima facie* case that the claims are not enabled. *See* M.P.E.P. (Eighth) § 2164.04 (2001).

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[1] The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 724 F. 2d 951, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 U.S.P.Q. 223 (Pat. Off. Bd. App. 1958).

B. Applicants' Description Enables All of the Claims

The Description enables claims 8-18 and 42-44, all ultimately dependent upon claim 1. Claim 1 is drawn to transfection particles comprising (i) one or more nucleic acid molecules, and (ii) identical or different covalently linked organic cationic molecules ionically associated with the nucleic acid molecules.

1. Enablement of Claims 8-18

Claims 8-18 further define the transfection particles of claim 1 and are drawn to compositions not limited to any one recited use. With respect to these claims, Applicants submit that to fully comply with the requirements of 35 U.S.C. § 112, first paragraph, the Description only needs to enable a person of ordinary skill in the art in making the claimed transfection particles and in using them in at least one manner. An enabling use can be, for example, an *in vitro* or *in vivo* application.

The Description enables one of ordinary skill in art *to make* the transfection particles of claims 8-18. A method of making the transfection particles is described from the fifth full paragraph on page 26 through the second full paragraph on page 28. The Description provides guidance including, for example, how to calculate the ratio of cationic precursor to nucleotide molecules (top of page 27), how long and at what temperature to complex the cationic precursors to the nucleotide molecules (page 27, bottom paragraph), under what conditions to affect oligomerization between cationic precursors (page 27, bottom paragraph), and how to monitor the formation of complexation (e.g., laser light scattering at bottom of page 27, CD and TEM methodologies are also describe on page 31). Guidance as to the cationic precursor molecules used to make the transfection particles is given, for example, from pages 5-6

and 8-18 in the Description. Guidance as to the nucleotide molecules used to make the transfection particles is given, for example, in pages 25-26 in the Description. Furthermore, working examples have been provided in the Description which further guides the skilled artisan in the manufacture of the transfection particles of claims 8-18 (e.g., pages 37-68).

The Description enables one of ordinary skill in the art *to use* the transfection particles of claims 8-18. For these claims to satisfy 35 U.S.C. § 112, first paragraph, the Description merely needs to enable the skilled artisan in any one use. In the last full paragraph at page 2 of the Description it is noted that "[t]he present invention provides particles for transfecting higher eucaryotic cells with nucleic acid molecules *in vitro* and *in vivo* comprising one or more nucleic acid molecules condensed by organic cationic molecules . . . ." As discussed *infra*, the skilled artisan is familiar with how to transfect cells *in vitro* using transfection particles without undue experimentation. Furthermore, working examples have been provided in pages 68-79 of the Description to further guide the skilled artisan in the use of the claimed transfection particles. These examples describe various aspects of the transfection method including concentrations and delivery technique. One of ordinary skill in the art would be able to take any of the transfection particles encompassed by claims 8-18 and perform without undue experimentation, for example, *in vitro* transfection as described in the Description.

2. Enablement of Claims 42-43

The Description also enables one of ordinary skill in the art *to make and use* the transfection particles as recited in claims 42-43. As described above, a determination of whether the Description enables the claims hinges on the scope of those claims. Claims 42 and 43 further define claim 1 and are drawn to pharmaceutical compositions comprising a pharmaceutically effective amount of transfection particles (i.e., compositions). Accordingly, these claims satisfy 35 U.S.C. § 112, first paragraph, if the Description enables a skilled artisan to make the compositions and use them in at least one manner.

As described *supra*, the Description enables the skilled artisan to make the transfection particles of claims 42-43. Moreover, the Description enables at pages 28-29 the skilled artisan to make the transfection particles having therapeutically active nucleotides. Examples of therapeutically active nucleotides include "antisense oligonucleotide[s] or a plasmid encoding a therapeutically active protein. . . . any sequence that is useful in therapy, e.g. somatic gene therapy or immunotherapy, may be used. Non-limiting examples are given in WO 93/07283." *See* Description, pages 28-29. The Description also enables the preparation of pharmaceutical formulations of the claimed transfection particles at page 29, in the second full paragraph.

The specification also enables the skilled artisan *to use* the compositions of claims 42 and 43. Several enabling *in vivo* uses are described, for example, in the Description at page 29: "Such pharmaceutical compositions may comprise transfection particles prepared freshly before administration. . . . Suitable additives are known in the art; reference is made to Remington's Pharmaceutical Sciences, 1980, for methods of

formulating pharmaceutical compositions. . . . In a preferred embodiment, the pharmaceutical composition is useful for intradermal application." As discussed *infra*, a skilled artisan would know how to formulate a pharmaceutical composition which can be administered, for example, intradermally. Furthermore, the Description provides the skilled artisan with additional guidance in the use of pharmaceutical formulations of the claimed transfection particles by way of providing *in vivo* working examples at pages 74-79.

3. Enablement of Claim 44

The Description also enables claim 44. Claim 44 is drawn to a method of introducing therapeutically active nucleic acid into a mammal, wherein a transfection particle of claim 1 is administered to said mammal intradermally. As described *supra*, the Description enables the skilled artisan to make a transfection particle having therapeutically active nucleic acid. Moreover, as described in the preceding paragraph, the Description enables the skilled artisan to administer the transfection particles intradermally. Applicants have provided the skilled artisan additional guidance in Examples 16-19 (pages 74-78) which indicates effective amounts (e.g., concentrations) and delivery techniques for *in vivo* applications.

B. The Examiner Has Not Made a Prima Facie Showing of Non-Enablement

As previously discussed, a patent applicant's specification disclosure which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d. 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). Here, Applicants submit that the Examiner has provided no evidence

that a skilled artisan would doubt the enablement of the claimed polynucleotides. The Examiner has not met her burden in explaining why the skilled artisan would not be enabled to practice the claimed invention throughout the entire scope of the claims.

1. Basis of Rejection of Claims 8-18

As a basis for the rejection of claims 8-18 under 35 U.S.C. § 112, first paragraph, the Examiner indicates that "[t]he art of transfection using lipophilic cationic molecules is unpredictable." Paper No. 11, p. 8. But Applicants' claims 8-18 are not drawn to a transfection methodology. Thus, the Description only needs to enable as to manufacture and at least one use of the claimed compositions. For the reasons discussed *supra*, the Description so enables.

The Examiner supports her allegation of nonenablement by pointing out that various references only list *particular* lipophilic cationic molecules used to form transfection particles. *Id.* (*citing* Zelphati *et al.*, "Cationic Liposomes as an Oligonucleotide Carrier: Mechanism of Action," *J. Liposome Res.* 7(1):31-49 (1997) ("Zelphati").) However, this is not a *prima facie* showing of unpredictability in the art. The mere fact that Zelphati and other references only list particular examples of useful lipophilic cationic molecules does not prove or suggest that Applicants' claimed lipophilic cationic molecules are not enabled.

The Examiner also generally alleges without support that lipophilic cationic molecules have unpredictable properties including "the ability of precursor cationic molecules to oligomerize based upon the extent of hydrophobic interactions, [and] compaction and encapsulation with nucleic acids, ..." Paper No. 11, p. 9. Applicants respectfully request that it be pointed out where these references indicate the

unpredictability of the art of transfection particle manufacture in general and manufacture of the claimed compositions in particular. Applicants' Description has enabled a class of cationic lipids capable of forming transfection particles; and further provided representative examples from this classification. Yet, the Examiner has provided no evidence to show that a person of ordinary skill in the art would doubt that the claimed compositions can be made and/or used.

Moreover, Zelphati *strengthens* Applicants' assertion. This reference states that "[i]n general, cationic lipids have enhanced oligonucleotide cell association in a time- and concentration-dependent manner." *See* Zelphati at 34. This passage implicates cationic lipids as generally capable of forming transfection particles with oligonucleotides. Moreover, this reference supports Applicants' assertion that the Description enables at least one use. In particular, Zelphati states that ". . . in all *in vitro* studies cationic liposomes have improved the potency of oligonucleotides." *Id.* at 43 (emphasis added). Applicants have asserted this use and provided working examples. *See supra.*

The Examiner has also stated that "applicants have not provided guidance in the specification or examples that would show by correlation the practice of the instant invention the capability of **all** the cationic molecules commensurate in scope with claims 8-18." Paper No. 11, p. 9, paragraph 2 (emphasis in original); see also paragraph 4. However, the USPTO has promulgated guidelines explicitly stating that

> [f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where

> adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

M.P.E.P. (Eighth) §2164.02 (Working Examples and a Claimed Genus) (2001). Here, the class of claimed molecules all share properties with the working examples (e.g., a cationic function for ionic interaction with nucleic acid, a lipophilic function, and a cross linking function to form covalent bonds with other molecules). The Examiner has not provided adequate reasons to suggest that one skilled in the art could not make and/or use every member of the class without undue experimentation.

Accordingly, Applicants respectfully request that the rejection of claims 8-18 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

2. Basis of Rejection of Claims 42-44

In making the enablement rejection of claims 42-44, the Examiner alleges that "[t]he prior art in the area of pharmaceutical use of cationic liposomes for nucleic acid delivery *in vivo* as a therapeutic agent is totally undeveloped." Applicants respectfully disagree. The pharmaceutical use of cationic liposomes for nucleic acid delivery *in vivo* is recognized: "Liposomes have proven useful for gene therapy. . . . This field was revived by the discovery that cationic lipids can condense DNA and increase transfection yields in vitro by several orders of magnitude. . . . Subsequently, reports on transfections in vivo stimulated intense interest in the use of liposomes for gene therapy. . . ." Lasic, D.D. *et al.*, "Liposomes Revisited," *Science, 267*:1275-1276 (1995) (*citing* references at page 1276, dating between 1986 and 1993; provided herewith as Exhibit A). Further use of cationic liposomes for nucleic acid delivery *in vivo* is found in the following: "Although *in vivo* transfection efficiency of the current cationic lipid-based gene delivery

systems is generally lower compared to viral vectors, this approach has proven useful in many *in vivo* applications in animal models . . . and more recently in human clinical trials . . . ." Mahato, R. I. *et al.*, "Cationic Lipid-Based Gene Delivery Systems: Pharmaceutical Perspectives," *Pharmaceutical Research, 14*(7):853-859 (1997) (see page 853, provided herewith as Exhibit B)

The Examiner alleges that the art in this field is unpredictable as to efficacy of the transfection particles. Paper No. 11, p. 11. However, the toxicity or targeting ability of the transfection particles need not be shown. *See* M.P.E.P. (Eighth) § 2164.01(c) (2001) ("The applicant need not demonstrate that the invention is completely safe."). As evidenced by the examples, there is an effect commensurate to the scope of the claims. *See* Description, Examples 17-19, pp. 75-78.

The Examiner also bases her rejection on the grounds that the Description has not enabled every transfection particles species in the scope of the genus claim: "[A]pplicants have not provided guidance in the specification or examples that would show by correlation the pharmaceutical usage or methods to achieve therapeutic effects with any of the claimed transfection particles." Paper No. 11, p. 12 (emphasis in original). As discussed in the preceding section, however, to allege that a genus claim is not enabled, the Examiner must provide specific evidence showing that the skilled artisan would not expect the claimed genus could be used in the claimed manner without undue experimentation. Applicants assert that the class of claimed molecules all share properties with the working examples (e.g., a cationic function for ionic interaction with nucleic acid, a lipophilic function, and a cross linking function to form covalent bonds with other molecules). Furthermore, the Description at pages 5-6, for example, also

enables the class of claimed transfection particles. The Examiner has not provided adequate reasons to suggest that one skilled in the art could not make and/or use every member of the class without undue experimentation.

The Examiner also bases her rejection on the grounds that "there is no Description or guidance within [Example 19] to demonstrate a therapeutic effect used in the prevention, diagnosis, alleviation, treatment or cure of disease." Applicants respectfully disagree that this can serve as a basis for a rejection under 35 U.S.C. § 112, first paragraph. The M.P.E.P. provides that "[c]ompliance with the enablement requirement . . . does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'" M.P.E.P. (Eighth) § 2164.02 (2001). Applicants' Description provides at pages 28-29 guidance to the skilled artisan that nucleotides conferring a therapeutic effect can be used with the invention as claimed. It would be apparent to the skilled artisan which nucleotides to use.

3. Exhibits

Applicants respectfully assert that the Examiner has not met her burden to show that the state of the art of making or using transfection particles is unpredictable. Assuming, *arguendo,* that the Examiner has met her burden, Applicants provide herewith references indicating that the Description would have enabled the skilled artisan.

A person of ordinary skill in the art enlightened by Applicant's Description would be able to make the claimed transfection particles. For example, the skilled artisan would recognize that "[c]ationic liposomes are the most widely and successfully used lipid-based vectors for gene transfer. . . . The preparation procedure is simple. The

cationic liposomes . . . are mixed with DNA in a dilute solution. The complexes form spontaneously due to electrostatic charge interactions, which lead to liposome fusion and aggregation." Maurer, N. *et al.*, "Lipid-based systems for the intracellular delivery of genetic drugs," *Molecular Membrane Biology, 16*:129-140 (1999) (emphasis added, see pages 130-131, provided herewith as Exhibit C).

Furthermore, it is well established amongst skilled artisans that "cationic lipids . . . have since become invaluable research tools *in vitro* . . . ." Schatzlein, A.G. "Non-viral vectors in cancer gene therapy: principles and progress," *Anti-Cancer Drugs, 12*:275-304, 276 (2001) (see page 276, provided herewith as Exhibit D). As discussed above, Zelphati also points to the recognition of cationic lipids for *in vitro* transfection (". . . in all *in vitro* studies cationic liposomes have improved the potency of oligonucleotides."). Furthermore, the skilled artisan at the time of Applicants' invention recognized that "[b]ecause of its convenience and efficacy, cationic lipid-mediated gene delivery technology has become a standard transfection technique for cultured cells." Felgner, P. L. *et al.*, "Improved Cationic Lipid Formulations for *In Vivo* Gene Therapy," *Annals New York Academy of Sciences, 772*:126-139 (1995) ("Felgner," see page 126, provided herewith as Exhibit E).

References provided in the preceding section (e.g., Exhibits A and B) also point to the fact that the skilled artisans recognize that cationic lipids are valuable for *in vivo* transfection as well. The Felgner reference also indicates that the skilled artisan at the time of Applicants' invention was familiar with therapeutic *in vivo* uses of cationic lipids: "There are many published reports on the use of cationic lipids of direct *in vivo* gene delivery." *See* Exhibit E, at page 134-135.

Thus, the skilled artisan at the time of Applicants' invention would recognize both *in vitro* and *in vivo* uses for the claimed transfection particles and methodologies. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 8-18 and 42-44 under 35 U.S.C. § 112, first paragraph.

III. Rejections under 35 U.S.C. § 112, second paragraph

Amendments have been made to claims 3, 4, 6-11, 13, 14, 22, 27-31, 46, and 47 to obviate the Examiner's rejections under 35 U.S.C. § 112, second paragraph. In particular, the term "function" (or its plural) in claims 3, 4, 6, 7, 28-31, 46 and 47 was changed either to "functionality" or "functional group" (or their respective plural forms) such that each term would refer to a property and not an action facilitated by the transfection particle. Claim 4 has been amended to clarify what the term "suitably" entails.

Applicants respectfully traverse the Examiner's rejection of claims 8-10, 13 and 14 under 35 U.S.C. § 112, second paragraph for use of the term "radical". Applicants submit that the meaning of "radical" is clear to the skilled artisan and provide herewith its definition from Grant and Hackh's Chemical Dictionary, 5th ed. (provided as Exhibit F). Hence, "radical" as used in the context of the claims in which it appears is understood to mean a "group of atoms which confers characteristic properties on a compound containing it, or which remains unchanged during a series of reactions. . . ." *See Id.* This meaning does not implicate free radical formation wherein the valency of an atom includes an electron without its orthogonal pair.

Applicants note that the term "suitably substituted" does not appear anywhere in claims 9 and 11. Accordingly, rejection of these claims for incorporation of such a term is improper.

Use of the terms "linkages" or "linked" in claims 22, 28 and 29 has been deleted or amended so as to ensure sufficient antecedent basis.

The term "carries" in claim 27 has been amended to "linked via one or more covalent bonds" to clarify the relationship between the transfection particle and the cellular targeting functionality.

Applicants also respectfully traverse the Examiner's rejection of claim 3 with regard to the assertion that the term "non-toxic" renders the claim indefinite and vague. The last full paragraph of page 7 of the description states that "[t]he requirements for the recipient backbone for detergent molecules according to the invention are obvious, convenient to prepare and non-toxic to cells." Hence, it would be clear to one of ordinary skill in the art that at useful dosages, the lipids would be non-toxic, that is non-lethal, to cells.

Applicants believe that all of the Examiner's rejections under 35 U.S.C. § 112, second paragraph, have been addressed or rendered moot. Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

IV. Rejections under 35 U.S.C. § 102

A. Rejection of Claims 1-6, 19, 22-29, 40, 41, 45 and 46

The Examiner rejected claims 1-6, 19, 22-29, 40, 41, 45 and 46 under 35 U.S.C. § 102(b) as being anticipated by Gershon. Paper No. 11, p. 3. The Examiner alleges that Gershon discloses all of the elements of claim 1, and in particular, the following:

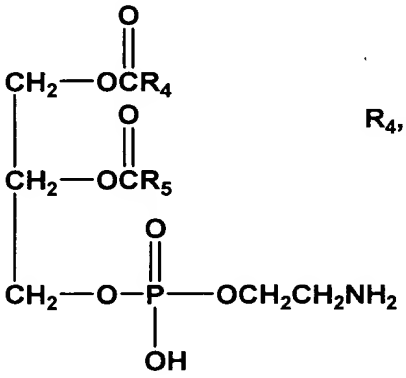
> Liposome formation was facilitated by oligomerization of the DOTMA and PE precursor molecules and DNA, RNA, and plasmid DNA encapsulation into said liposomes was achieved without crosslinking . . . . Both DOTMA and PE comprise of [sic] at least one functionality for binding to the same or different precursor molecules . . . .

Paper No. 11, p. 5. Applicants respectfully traverse the rejection.

Claim 1 is drawn to a transfection particle comprising (i) one or more nucleic acid molecules; and (ii) identical or different organic cationic precursor molecules linked to each other via one or more covalent bonds; wherein the precursor molecules are complexed to the nucleic acid molecules without crosslinking nucleic acid molecules. Claims 2-6, 19, 22-29, 40, 41, 45 and 46 depend directly or indirectly on claim 1 and thus comprise the elements recited above. Claim 1 requires that the precursor molecules are linked to each other via one or more covalent bonds. These bonds are formed by, for example, air induced dimerization. Description pp. 4-5. The Description lists a number of non-limiting examples of chemical functionalities capable of forming these covalent bonds: "thiol residues that react to provide disulfide bridges (-S-S-), acid hydrazides and aldehydes that provide hydrazones (-C=N-N-), amines and aldehydes that provide Schiff bases (imines, -C=N-), and amines that react with ethylene residues that are suitably substituted (e.g. halides) to provide enamines (-C=C-N-)." Description p. 6. Although DOTMA or PE may form liposomes, such an oligomerization does not include the

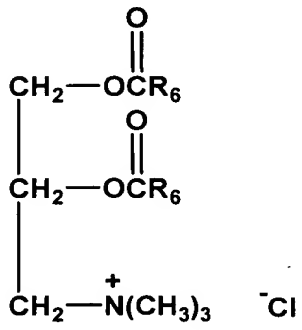
formation of any covalent bonds. Rather, the lipophilic groups of these molecules associate via non-covalent interactions such as van der Waals forces. *See* Ege, S., *Organic Chemistry*, 2d ed., pp. 24-29 & 612-613 (1989) (Exhibit G). Moreover, it is clear from the structures provided below that neither DOTMA or PE have any such functionalities capable of forming covalent bonds upon exposure to air.

PE (Phosphatidylethanolamine)



R_4, R_5 = long chain alkyl

DOTMA (N-[1-[2,3-bis(oleoyloxy)]propyl]-N,N,N-trimethylammonium chloride)



R_6 = long chain alkyl

The above lipophilic molecules do not form covalent bonds with other PE or DOTMA molecules under the reaction conditions employed by Gershon. Thus, Gershon does not anticipate claim 1 or its dependent claims 2-6, 19, 22-29, 40, 41, 45 and 46. Accordingly, Applicants respectfully request that the rejection of claims 1-6, 19, 22-29, 40, 41, 45 and 46 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

B. Rejections of Claims 7, 20, and 30-33

The Examiner rejected claims 7, 20, and 30-33 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,705,693; Yoshikawa *et al.*, *FEBS Letters, 396*:71-76 (1996); and U.S. Patents Nos. 5,736,392 and 6,051,429 respectively. Applicants respectfully traverse the rejection.

Claims 7, 20, and 30-33 ultimately depend from claim 1. Thus, they are also drawn to transfection particles comprising (i) one or more nucleic acid molecules, and (ii) identical or different covalently linked organic cationic molecules ionically associated with the nucleic acid molecules. However, U.S. Patent Nos. 5,705,693 ("the '693 patent"); 5,736,392 ("the '392 patent) and 6,051,429 ("the '429 patent); and Yoshikawa *et al.*, *FEBS Letters, 396*:71-76 (1996) ("Yoshikawa") do not discuss the one or more covalent bonds as required by claim 1.

The '693 patent generally discuss the use of cationic lipids complexed to oligonucleotides for purposes of cellular transfection (see Abstract). Although this patent discusses a variety of cationic lipid molecules (e.g., columns 1-2 and 5), these molecules are missing the required chemical functional group needed for forming intermolecular covalent bonds, as recited by Applicants' claim 1. Nor would there be any motivation to form covalent bonds between the molecules taught by the '693 patent.

Yoshikawa discusses the use of dioctadecylamidoglycylspermine (DOGS) to complex with DNA for purposes of cellular transfection. The structure of DOGS is shown in Scheme 1 on page 72. It is apparent from the structure of this molecule that this reference does not teach the required chemical functional group needed for forming intermolecular covalent bonds, as recited by Applicants' claim 1. Nor would there be any motivation to form covalent bonds between the DOGS molecules taught by Yoshikawa.

The '392 and '429 patents generally discuss the use of cationic lipids complexed to DNA for purposes of cellular transfection (see Abstract). Although a variety of cationic lipid molecules are discussed (e.g., see the '392 patent, column 3, lines 53-65), these patents do not mention the required chemical functional group needed for forming intermolecular covalent bonds, as recited by Applicants' claim 1. Nor would there be any motivation to form covalent bonds between the cationic molecules taught by these patents.

Because the references cited by the Examiner do not teach one or more of the elements required by Applicants' claim 1, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

1. (Amended) A particle for transfecting higher eucaryotic cells with nucleic acid molecules *in vitro* and *in vivo* comprising one or more nucleic acid molecules condensed by organic cationic molecules, said particle [particles] being obtained by (1) condensing said one or more [complexing the] nucleic acid molecules with identical or different organic cationic precursor molecules without crosslinking any of said one or more nucleic acid molecules, and (2) thereafter [covalently] linking the precursor molecules to each other with one or more covalent bonds on the condensed one or more nucleic acid molecules [template].

3. (Amended) The transfection particle of claim 2, wherein the cationic detergent precursor molecules comprise:

a) at least one functional group [function] for binding to one or more other detergent molecules,

b) at least one lipophilic residue,

c) a non-toxic recipient backbone,

d) a cationic group for binding to nucleic acid molecules.

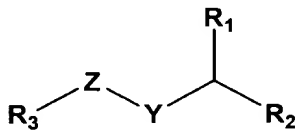
4. (Amended) The transfection particle of claim 3, wherein the functional group [function] of the cationic precursor detergent molecules for binding to other detergent molecules is a dimerizable or polymerizable functional group [function] selected from the group consisting of thiols, acid hydrazides, aldehydes, amines, and ethylene residues that are suitably substituted to provide enamines upon reaction with an amine.

5. (Amended) The transfection particle of claim 4, wherein the lipophilic residue is selected from the group consisting of lipophilic amides, esters [or] and ethers.

6. (Amended) The transfection particle of claim 3, wherein the functional group [function] for binding to nucleic acid molecules is selected from an amine or derivative thereof.

7. (Amended) The transfection particle of claim 6, wherein the functional group [function] for binding to nucleic acid molecules is guanidine.

8. (Amended) The transfection particle of claim 1, wherein the organic cationic precursor molecule is represented by general formula I



(I)

wherein

R_1 denotes (C_1-C_{10}-alkylene)-SH, wherein the alkylene radical may represent a straight chained or branched hydrocarbon;

R_2 denotes $-NR_4R_5$, $-NHR_4R_5^+$, $-N(R_4)_2R_5^+$, $-C(=NR_4)NR_5R_6$, $-C(=X)-C_1$-C_{10}-alkylene, wherein the alkylene radical may represent a straight chained or branched hydrocarbon and may be substituted by up to four dialkyl amino groups or a thiomonosaccharide;

R_3 denotes C_5-C_{30}-alkyl, straight chained or branched and optionally substituted [preferably] with one or more halogen [atom(s)] atoms or dialkyl amino [group(s)] groups, or

C_5-C_{30}-alkenyl, straight chained or branched having up to ten C=C-double bonds and is optionally substituted [preferably] with one or more halogen [atom(s)] atoms or dialkyl amino [group(s)] groups, or

C_5-C_{30}-alkynyl [C_5-C_{30}-alkinyl], straight chained or branched having up to ten C≡C-triple bonds and is optionally substituted [preferably] with one or more halogen [atom(s)] atoms or dialkyl amino [group(s)] groups, or

C_6-C_{10}-aryl optionally substituted, or

C_7-C_{16}-aralkyl optionally substituted, or a

C_5-C_{30}-alkyl-chain interrupted by up to 10 amino groups $-NR_4-$ and having optionally an amino-group which is optionally substituted by an amino acid;

R_4, R_5 and R_6 denote independently from each other hydrogen or

C_1-C_4-alkyl;

X denotes O or S;

Y denotes C=O or C=S and

Z denotes O, S or $-NR_4-$.

9. (Amended) The transfection particle of claim 8, wherein the cationic precursor molecules correspond to general formula I, wherein

R_1 denotes (C_1-C_6-alkylene)-SH, wherein the alkylene radical may represent a straight chained or branched hydrocarbon;

R_2 denotes $-NR_4R_5$, $-NHR_4R_5^+$, $-N(R_4)_2R_5^+$, $-C(=NR_4)NR_5R_6$, -C(=X)-C_1-C_4-alkylene, wherein the alkylene radical may represent a straight chained or branched hydrocarbon and may be substituted by up to four amino radicals $-NR_4R_5$ or a thiomonosaccharide;

R_3 denotes C_5-C_{20}-alkyl, straight chained or branched and optionally substituted [preferably] with F, Cl, Br or $-NR_4R_5$, or

C_5-C_{20}-alkenyl, straight chained or branched having up to five C=C-double bonds and is optionally substituted [preferably] with F, Cl, Br or $-NR_4R_5$, or

C_5-C_{20}-alkynyl [C_5-C_{20}-alkinyl], straight chained or branched having up to five C≡C-triple bonds and is optionally substituted [preferably] with F, Cl, Br or $-NR_4R_5$, or

C_6-C_{10}-aryl optionally substituted [preferably] with C_1-C_4-alkyl, F, Cl, Br or $-NR_4R_5$, or

C_7-C_{14}-aralkyl optionally substituted [preferably] with C_1-C_4-alkyl, F, Cl, Br or $-NR_4R_5$, or

a C_5-C_{20}-alkyl chain interrupted by up to 10 amino groups $-NR_4-$ and having optionally [a -amino-group] an amino group which is optionally substituted by an amino acid;

R_4, R_5 and R_6 denote independently from each other hydrogen or C_1-C_4-alkyl;

X denotes O or S;

Y denotes C=O or C=S and

Z denotes O, S or $-NR_4-$.

10. (Amended) The transfection particle of claim 8, wherein the cationic precursor molecules correspond to general formula I, wherein

R_1 denotes (C_1-C_4-alkylene)-SH, wherein the alkylene radical may represent a straight chained or branched hydrocarbon;

R_2 denotes $-NR_4R_5$, $-NHR_4R_5^+$, $-N(R_4)_2R_5^+$, $-C(=NR_4)NR_5R_6$, $-C(=X)-C_1$-C_4-alkyl, wherein the alkyl radical may represent a straight chained or branched hydrocarbon and may be substituted by up to four amino radicals $-NR_4R_5$, or a thiomonosaccharide;

R_3 C_5-C_{12}-alkyl, straight chained or branched and optionally substituted [preferably] with F, Cl, Br or $-NH_2$, or a C_5-C_{15}-alkyl chain interrupted by up to 7 amino groups $-NR_4-$ and having optionally [a -amino-group] an amino group which is optionally substituted by the amino acid cysteine;

R_4, R_5 and R_6 denote independently from each other hydrogen or methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl or [tert.-butyl] tert-butyl;

X denotes O or S;

Y denotes C=O or C=S and

Z denotes O, S or $-NR_4-$.

11. (Amended) The transfection particle of claim 8, wherein the cationic precursor molecules correspond to the general formula I, wherein

R_1 denotes $-CH_2-SH$;

R_2 denotes $-NH_2$, $-NH_3^+$, $-C(=N^+H_2)NH_2$, $-C(=O)-C_1-C_4$-alkyl straight chained or branched and optionally substituted with F, Cl, Br or $-NH_2$, or an ornithine radical or a S-galactosyl radical;

R_3 denotes a C_6-C_{15}-alkyl radical straight chained or branched and optionally substituted [preferably] with F, Cl, Br or $-NH_2$;

Y denotes C=O;

Z denotes O or -NH-.

22. (Amended) The transfection particle of claim 1, wherein the one or more covalent bonds [linkage] between the cationic molecules are [is] degradable under cellular conditions.

27. (Amended) The transfection particle of claim 1, characterized in that it is linked via one or more covalent bonds to [carries] one or more cellular targeting functionalities [functions] and/or one or more functionalities [functions] capable of facilitating endocytosis.

28. (Amended) The transfection particle of claim 27, wherein said functionalities [functions] are linked via said one or more covalent bonds to the cationic molecules.

29. (Amended) The transfection particle of claim 27, wherein said functionalities [functions] are linked via said one or more covalent bonds to nucleic acid binding molecules that are present in addition to the cationic molecules.

30. (Amended) The transfection particle of claim 27, wherein the targeting functionality [function] is a cellular protein ligand.

31. (Amended) The transfection particle of claim 27, wherein the targeting functionality [function] is a sugar residue.

46. (Amended) The kit of parts of claim 45 comprising in addition or more functionality [functions] for cellular targeting.

47. (Amended) The kit of parts of claim 45 comprising in addition one [once] or more endosomolytic functionalities [functions].

Claim 48 is newly added.